UCL-Tohoku Organic Symposium

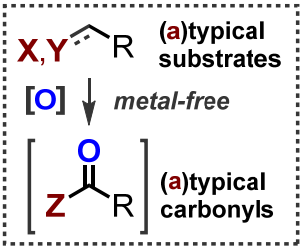
Aoba Science Hall (東北大学)

Hosts: Yujiro HAYASHI / Takeaki IWAMOTO

Atypical Oxidative Methods to (A)Typically Activated Esters

MLear@lincoln.ac.uk
Reader, School of Chemistry

Joseph Banks Laboratories
College of Science
University of Lincoln
Lincoln, United Kingdom



1

First, *Foremost* THANKS

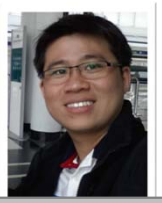
(林 雄二郎 教授)


Dan Edwards


Matt Wadlow


Charlie Keen


Yujiro Hayashi


Stanley Eey

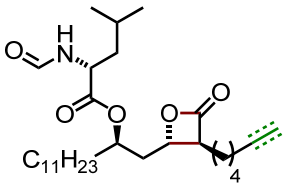

Luke Williams


Louis Adriaenssens

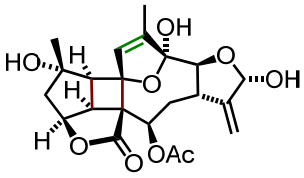

Jing Li

2

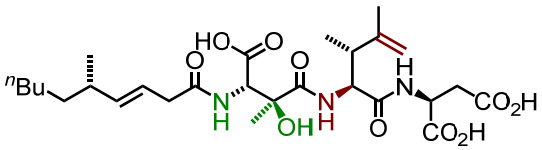
Some *Natural Targets* Investigated



tetrahydrolipstatins
(Analogue probe synthesis:
e.g. JACS **2010**, *132*, 656)



bielschowskysins
(Synthetic studies:
e.g. TL **2013**, *54*, 4406)



lipopeptides
(Total (de novo) synthesis:
Org. Lett. **2012**, *14*, 1560)

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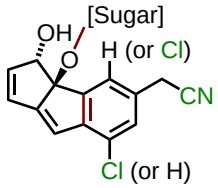
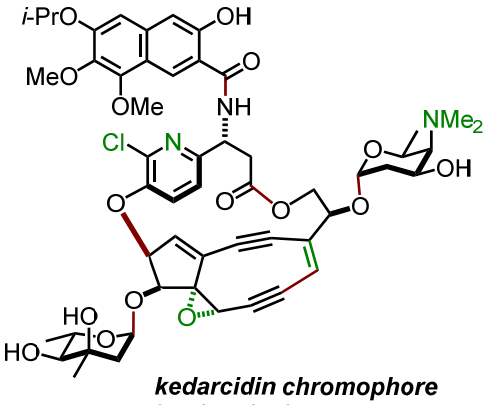
Some *Natural Targets* Investigated



cyanosporasides
(Biomimetic synthesis:
Angew. **2014**, *53*, 13902)



kedarcidin chromophore
(Total synthesis:
Chem. Sci. **2018**, in prep.)

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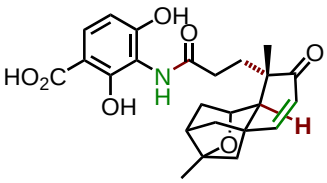
The *Inspiration for* Today



Platensimycin
(**total synthesis:** *Chem. Eur. J.* **2014**, 11556)

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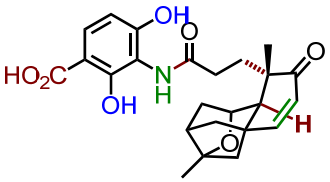
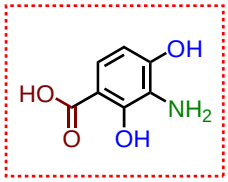
Inspiration for Today Platensimycin



Platensimycin



aromatic polar domain

- Discovered by Singh, Wang & Soisson *et al.* of Merck from *Streptomyces platensis* South African soil sample.
- Contains an architecturally unprecedented tetracyclic framework and an **uncommon aromatic polar domain**.

a) Wang. J.; Soisson, S. M. *et al. Nature* **2006**, *441*, 358-361;
b) Singh *et al. J. Am. Chem. Soc.* **2006**, *128*, 11916-11920.

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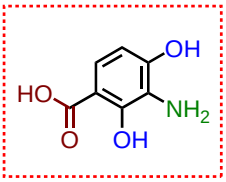
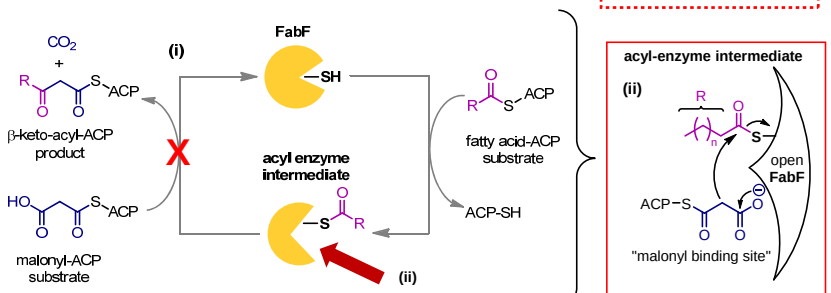
Mode of Action
MoA

- Targets **Type II fatty-acid biosynthesis** (FASII).
- Inhibits β-ketoacyl-(acyl-carrier-protein (ACP)) synthase I (**FabF**)





FabF inhibition in FASII by **Platensimycin**

Brown, E. D. *Nature* **2006**, 441, 293-294.

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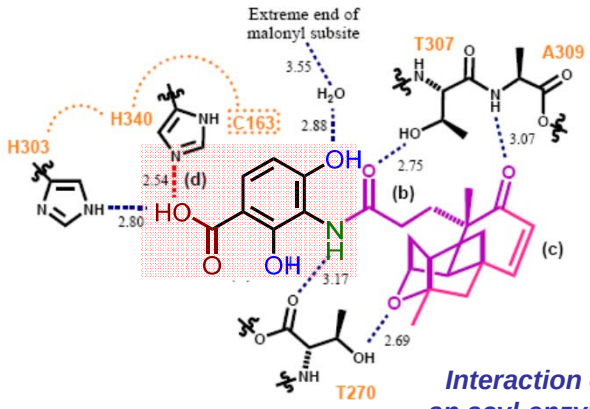
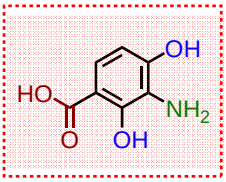
Binding
Model





Interaction of platensimycin with an acyl-enzyme intermediate model

Brown, E. D. *Nature* **2006**, 441, 293-294.

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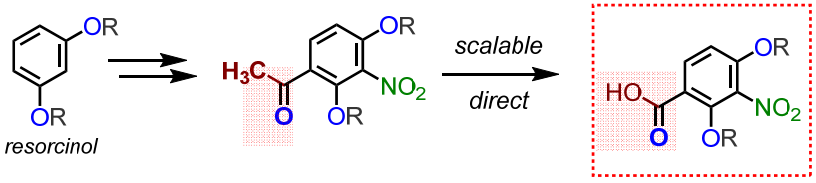
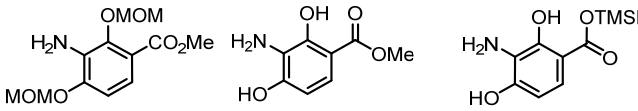
Need *Practical* Oxidation Method





Nicolaou: **36% (5 steps)** *Angew.* **2006**, *45*, 7086

Giannis: **28% (2 steps)** *Synthesis* **2007**, 2614.

Nicolaou: **17% (3 steps)** *Angew.* **2008**, *47*, 1780

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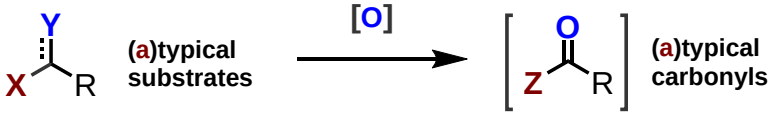
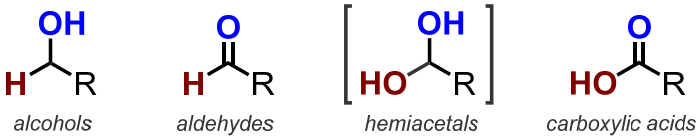
Oxidative *Methods* Typical Substrates



(a)typical substrates → **(a)typical carbonyls**



alcohols *aldehydes* *hemiacetals* *carboxylic acids*

typical starting materials

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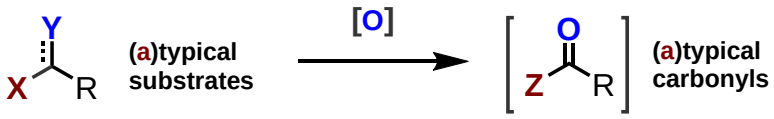
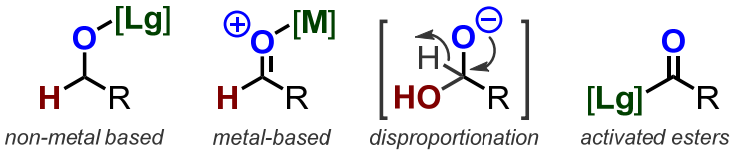
Oxidative *Methods*
Typical Mechanisms





typical mechanisms

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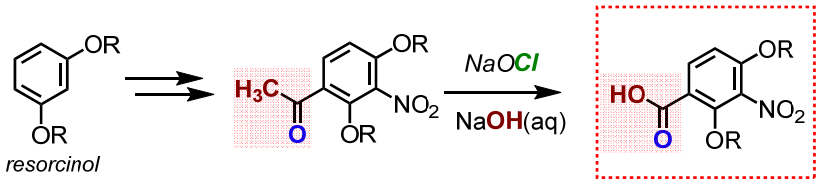
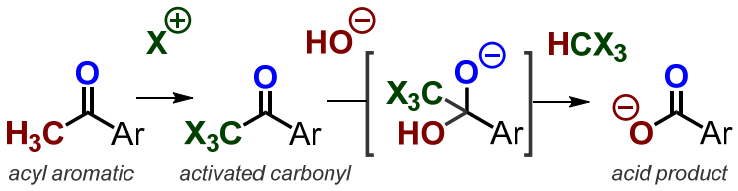
Oxidative *Methods*
Lieben Haloform





need protected ester product directly

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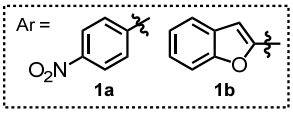
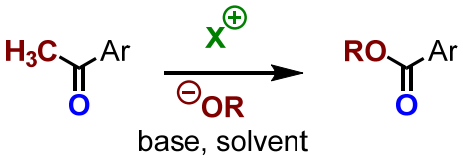
Oxidative *Methods*
Modified Haloform

Ar = 



entry	**1**	X^+(*eq.*)	base (*eq.*)	solvent	t	Yield (%)
1	**1a**	I_2 (*3*) or Br_2 (6)	pyridine (*6*)	MeOH	16h	65–67
2	**1a**	I_2 (*3*)	NaOMe (*6*)	MeOH	3h	54
3	**1a**	^{t}BuOCl (*6*)	pyridine (*6*)	MeOH	16h	33
4	**1a**	^{t}BuOCl (*6*)	DBU (*6*)	MeOH	16h	-
5	**1a**	^{t}BuOCl (*6*)	NaOMe (*6*)	MeOH	20min	78
6	**1a**	^{t}BuOCl (*6*)	NaOEt (*6*)	EtOH	20min	82
7	**1a**	^{t}BuOCl (*6*)	NaOMe (*6*)	MeOH	20min	95
8	**1a**	^{t}BuOCl (*3.5*)	NaOMe (*4*)	MeOH	<30s	99
9	**1b**	^{t}BuOCl (*3.5*)	NaOMe (*4*)	MeOH	<30s	98

Eey, Lear, Adriaenssens et al. *unpublished work*

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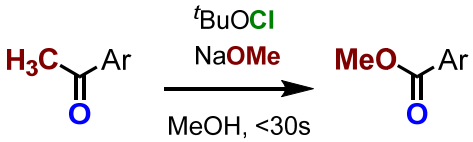
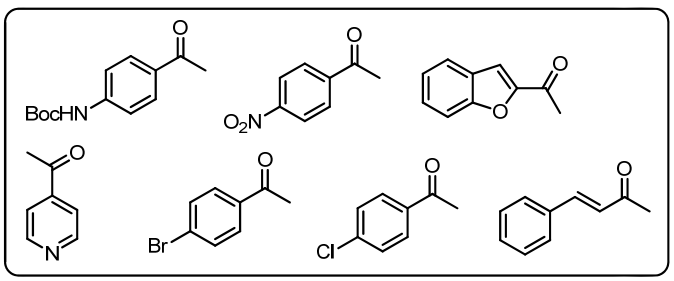
Oxidative *Methods*
Modified Haloform





4-6 equiv. ^{t}BuOCl/NaOMe 82% - 99% **Electronically poor substrates**

Eey, Lear, Adriaenssens et al. *unpublished work*

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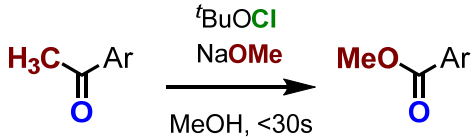
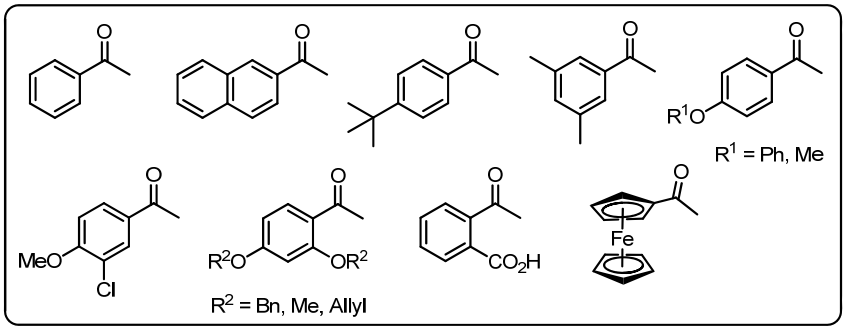
Oxidative *Methods*
Modified Haloform





12-20 equiv. ^{t}BuOCl/NaOMe (85% - 99%)

Electronically neutral to rich substrates

Eey, Lear, Adriaenssens et al. *unpublished work*

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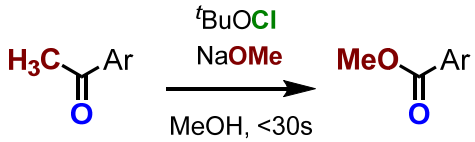
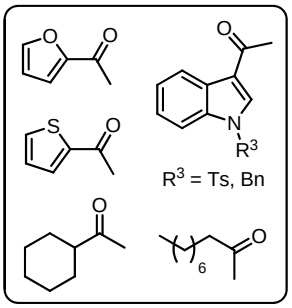
Oxidative *Methods*
Modified Haloform



Some tricky substrates



31-53% yields

Eey, Lear, Adriaenssens et al. *unpublished work*

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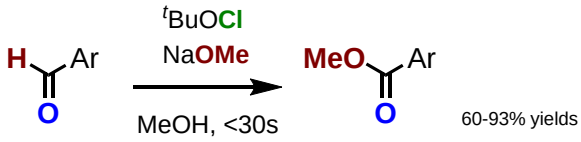
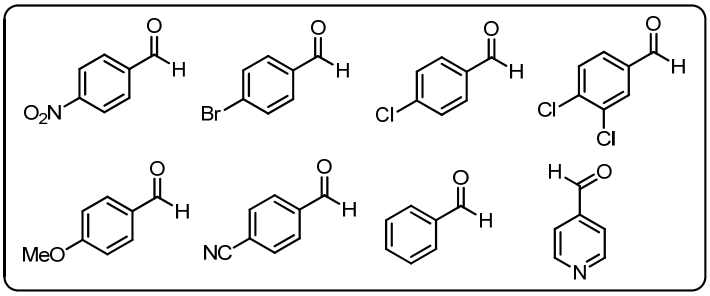
Oxidative *Methods*
Aryl Aldehydes



60-93% yields



Scope being explored and expanded

Eey, Lear, Adriaenssens et al. *unpublished work*

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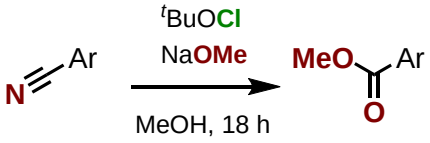
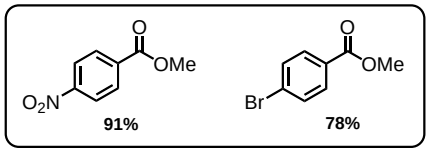
Oxidative *Methods*
Aryl Nitriles





Acid catalysis and heat are usually required for the transformation of nitriles to esters

Eey, Lear, Adriaenssens et al. *unpublished work*

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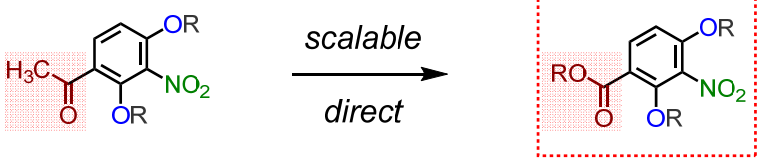
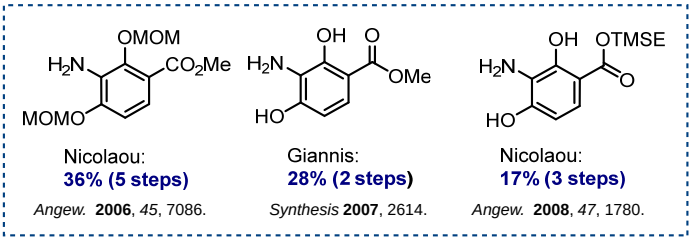
Application to Synthesis





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Eey, Lear *Chem. Eur. J.* **2014**, 11556

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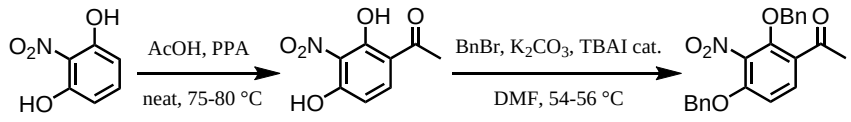
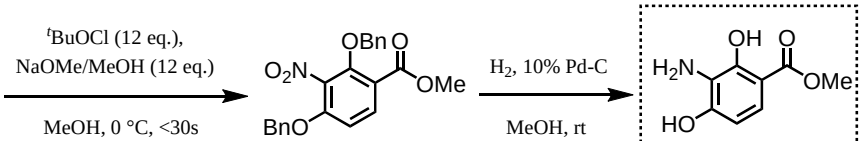
Application to Synthesis



2-nitroresorcinol **69%** **1** **95%** **2** (240 mg)



95% **3** **92%** *clean conversion* **4**

57% (4 steps)

Eey, Lear *Chem. Eur. J.* **2014**, 11556

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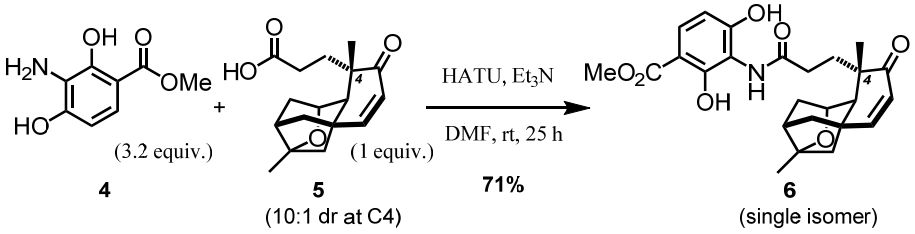
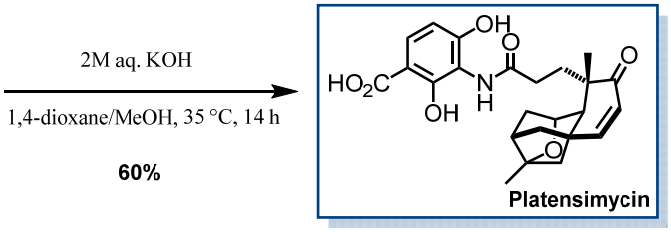
Application to Total Synthesis





21 steps, 2% overall from eugenol

Eey, Lear *Chem. Eur. J.* **2014**, 11556

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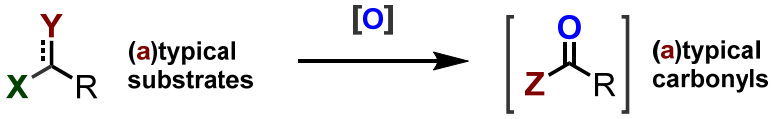
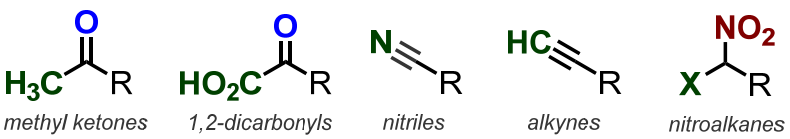
Oxidative *Methods* Less Typical Substrates





less typical starting materials (metal oxidants mostly used)

J. W. Bode et al., *Nature* **2011**, *480*, 471.

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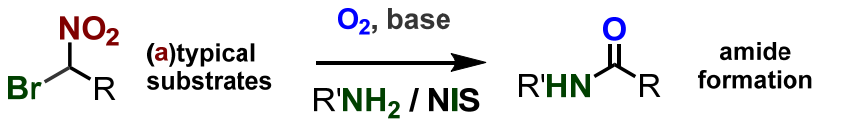
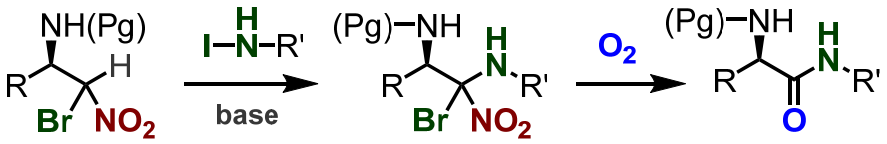
Oxidative *Methods*
Amide Formation

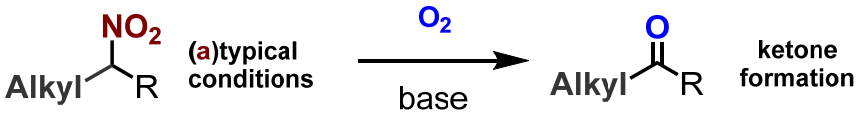


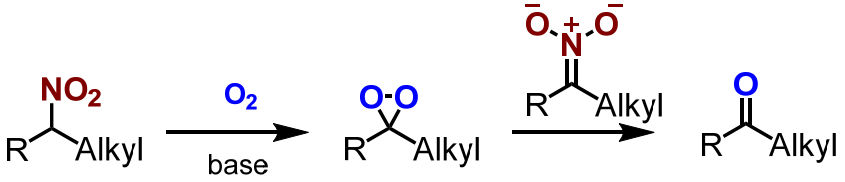


atypical "umpolung" mechanism proposed

J. N. Johnston et al., *Nature* **2010**, *465*, 1027

Oxidative *Methods*
Ketone Formation

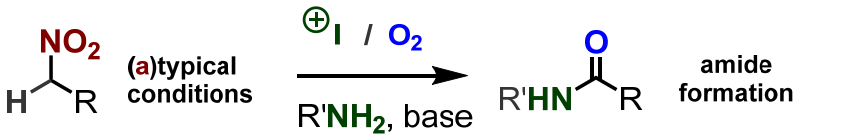


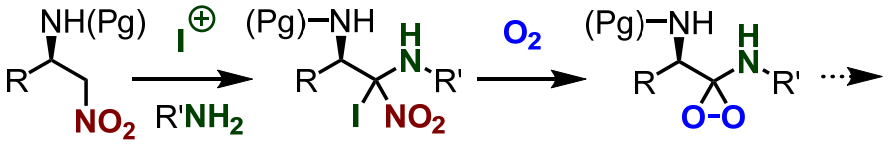


atypical Nef mechanism proposed

Umemiya, Hayashi et al., *Chem. Eur. J.* **2014**, *20*, 15753.

Oxidative *Methods*
Proposal





halogenative-amine-displacement mechanism *via* dioxirane proposed

Li, Lear, Hayashi et al., *Angew.* **2015**, *54*, 12986

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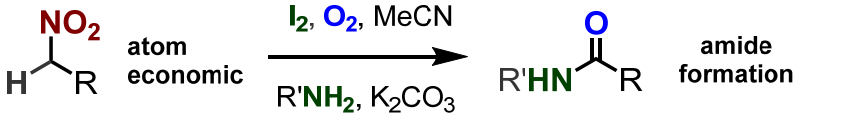
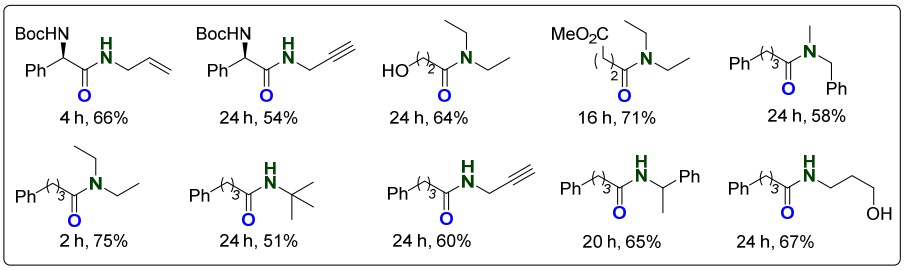
Oxidative *Methods*
Wide scope





Li, Lear, Hayashi et al., *Angew.* **2015**, *54*, 12986

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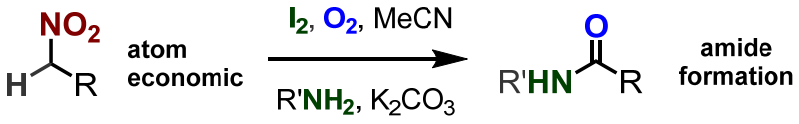
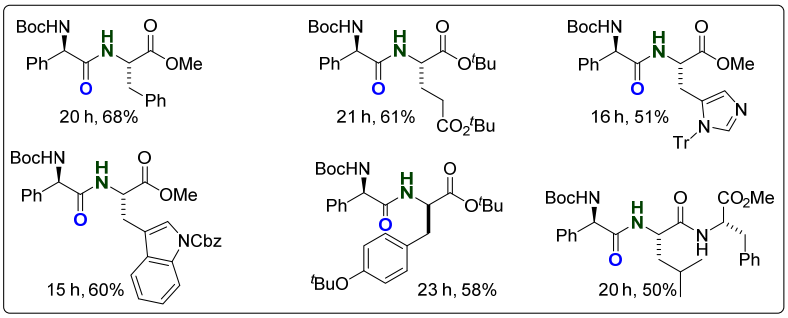
Oxidative *Methods*
Wide scope





Li, Lear, Hayashi et al., *Angew.* **2015**, *54*, 12986

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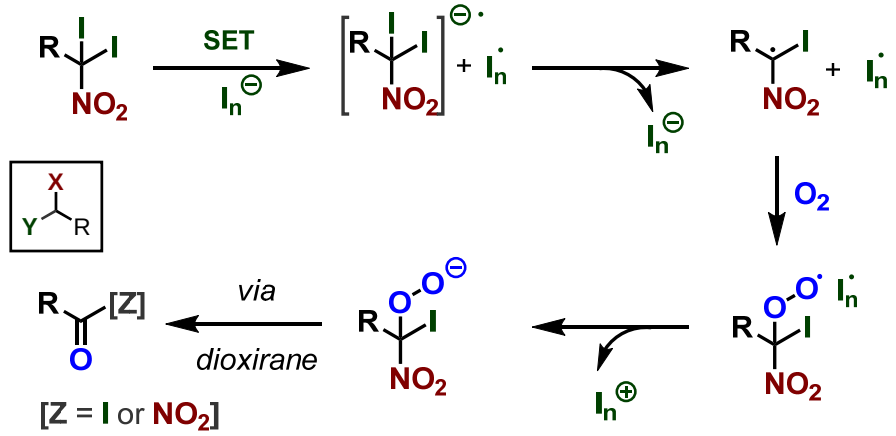
Oxidative Proposal *via*
Di-iodo, nitroalkanes



Li, Lear, Hayashi et al., *Angew.* **2015**, *54*, 12986; *Chem. Eur. J.* **2016**, *22*, 5538

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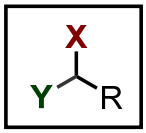
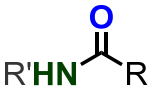
Oxidative *Methods*
Proposal



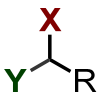
(a)typical conditions

O_2

R'NH_2, base



amide formation



X, **Y** = NO_2, SO_2Ar, $PO(OR)_2$, CN, OTs

explore different X, Y groups that are $1e^-$ and $2e^-$ stabilising

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Oxidative *Methods*
Malononitriles

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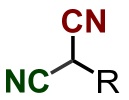
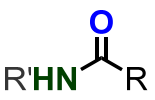


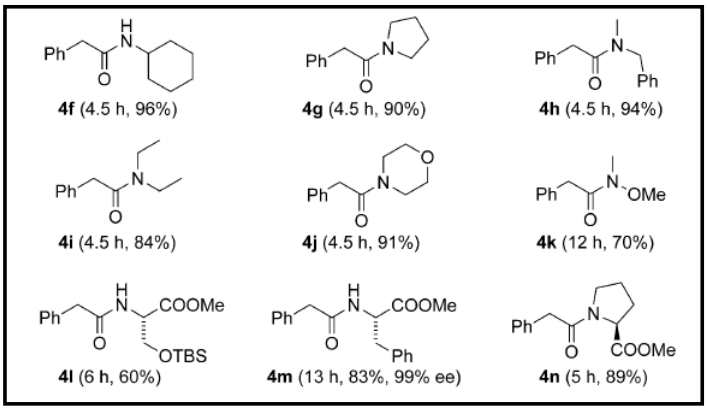
dicyano substrates

O_2, MeCN, rt

R'NH_2, K_2CO_3



amide formation



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Oxidative *Methods*
Challenging Substrates

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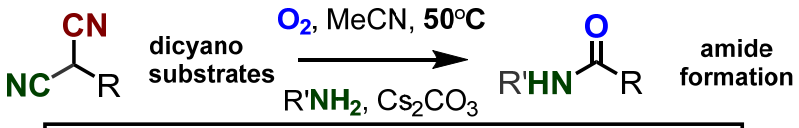

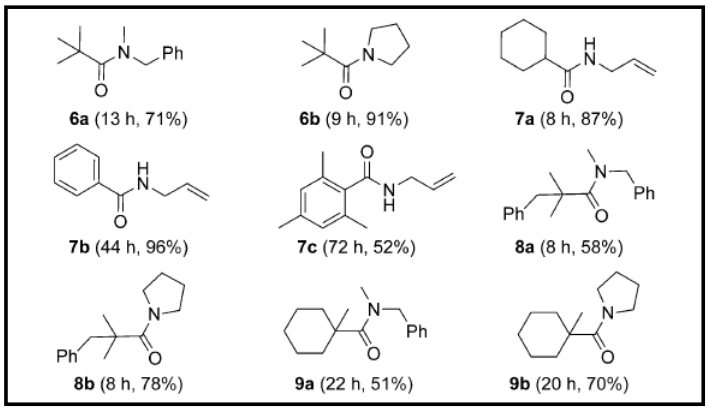

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Oxidative *Methods*
Proposed Mechanism

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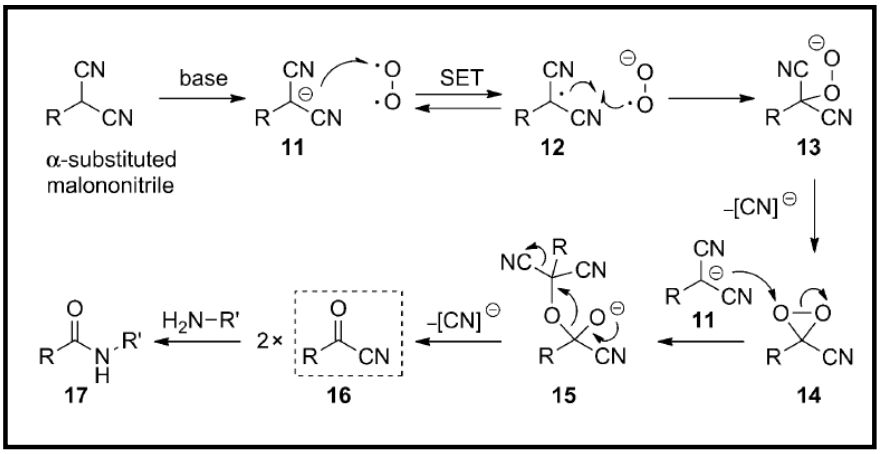

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(Lincoln, UK)